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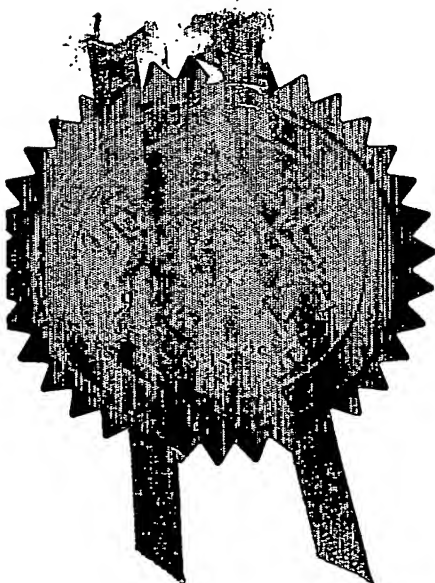
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**1/77**

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1. Your Reference	KC/PG4890		
2. Patent application number (The Patent office will fill in this part)	0224774.0		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB		
Patents ADP number (if you know it)	473587003.		
If the applicant is a corporate body, give the country/state of its corporation	GB		
4 Title of the invention	COMPOUNDS		
5 Name of your agent (if you know one)	KAREN CRAWLEY		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY (CN9 25.1) 980 GREAT WEST ROAD BRENTFORD MIDDLESEX TW8 9GS		
Patents ADP number (if you know it)	8072555006.		
6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of Filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body.	YES		

see note (d))

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Claim(s)	6
Abstract	1
Drawing(s)	-

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Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patent Form 9/77*)

Request for substantive examination (*Patent Form 10/77*)

Any other documents  
(please specify)

11.



I/We request the grant of a patent on the basis of this application

Signature WENDY FILLER  
AGENT FOR THE APPLICANTS

24 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

AMANDA WILKINSON

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## COMPOUNDS

### FIELD OF THE INVENTION

- The present invention relates to novel acyl pyrrolidine derivatives useful as anti-viral agents. Specifically, the present invention involves novel HCV inhibitors.

### BACKGROUND OF THE INVENTION

- Ikeda et al, (1997) Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry 22: 3339-3344 and Sato et al, (1995) Journal of the Chemical Society, Perkin Transactions 1, 14:1801-1809 and Sato et al, (1994) Heterocycles 37(1): 245-248 disclose 4',5'-unsubstituted acyl pyrrolidine compounds useful as reagents in the regioselective synthesis of bridged azabicyclic compounds; no medical use was disclosed for the acyl pyrrolidine compounds.
- Ikeda et al, (1996) Heterocycles 42(1): 155-158 and Confalone et al, (1988) Journal of Organic Chemistry 53(3): 482-487 and De Martino et al, (1976) Farmaco, Ed. Sci. 31(11): 785-790 disclose 4',5'-unsubstituted acyl pyrrolidine compounds useful as reagents in the synthesis of tricyclic nitrogen-containing heterocycles; no medical use was disclosed for the acyl pyrrolidine compounds. Alig et al, (1992) Journal of Medicinal Chemistry 35(23): 4393-4407 discloses a 4',5'-unsubstituted acyl pyrrolidine compound useful as a reagent in the synthesis of non-peptide fibrinogen receptor antagonists; no medical use was disclosed for the acyl pyrrolidine compound.
- Padwa et al, (1992) Journal of the American Chemical society 114(2): 593-601 discloses a 4',5'-unsubstituted acyl pyrrolidine compound useful as a reagent in the synthesis of azomethine ylides; no medical use was disclosed for the acyl pyrrolidine compound. Culbertson et al, (1990) Journal of Medicinal Chemistry 33(8): 2270-2275 and Crooks et al, (1979) Journal of the Chemical Society, Perkins Transactions 1, 11: 2719-2726 disclose 4',5'-unsubstituted acyl pyrrolidine compounds useful as reagents in the synthesis of 7-spiroamine quinolone and spiro[indan-2,2'-pyrrolidine] compounds respectively; no medical use was disclosed for the acyl pyrrolidine compounds.
- WO2002/44168, WO96/33170 and EP505868A2 disclose 4',5'-unsubstituted acyl pyrrolidine compounds useful as intermediates in the synthesis of indolecarboxamide, N-aroylamino acid amide and N-acyl- $\alpha$ -amino acid derivatives respectively; no medical use was disclosed for the acyl pyrrolidine compounds.
- De Caprariis et al, (1989) Journal of Heterocyclic Chemistry 26(4): 1023-1027 discloses 3 pyrrolidinedicarboxylic acid derivatives useful as intermediates in the synthesis of pyrrolid[1,4]benzodiazepine compounds; no medical use was disclosed for the pyrrolidinedicarboxylic acid derivatives.

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at \$5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K.L. (1997) *Hepatology* 26 (suppl 1): 71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of those treated, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon, both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) *Science* 244:359-362), hepatitis C virus (HCV) is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo, G et al (1989) *Science* 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae*, such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) *Science* 244:359-3; Miller, R.H. and R.H. Purcell (1990) *Proc. Natl. Acad. Sci. USA* 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al 'An RNA pseudoknot is

an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' RNA- A Publication of the RNA Society. 1(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) Virology 2<sup>nd</sup> Edition, p931-960; Raven Press, N.Y.). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. et al (1996) J. Virology 70:3363-3371; Tanaka, T. et al (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. et al (1996) J. Virology 70:3307-3312; Yamada, N. et al (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. et al (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.* (2000) Journal of Virology, 74(4), p.2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to cure HCV infection.

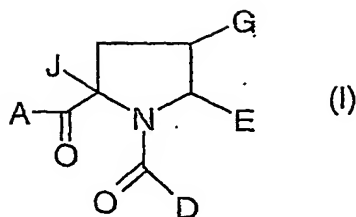
Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV.

#### SUMMARY OF THE INVENTION

The present invention involves acyl pyrrolidine compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and use of the compounds in treating viral infection, especially HCV infection.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of Formula (I) :



wherein:

A represents hydroxy;

5 D represents aryl or heteroaryl;

E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

10 G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

15 R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and heteroaryl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

20 R<sup>4</sup> is selected from the group consisting of C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; and

25 J represents C<sub>1-6</sub>alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl;

30 for use in medical therapy.

There is provided as a further aspect of the present invention a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof for use in human or veterinary

35 medical therapy, particularly in the treatment or prophylaxis of viral infection, particularly HCV infection.

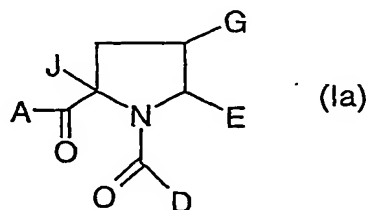
It will be appreciated that reference herein to therapy and/or treatment includes, but is not limited to prevention, retardation, prophylaxis, therapy and cure of the disease. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection includes treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

According to another aspect of the invention, there is provided the use of a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with viral infection, particularly HCV infection, which method comprises administering to said human or animal subject an effective amount of a compound of Formula (I) or a physiologically acceptable salt, solvate or ester thereof.

It will be appreciated that the compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. All of these racemic compounds, enantiomers and diastereoisomers are contemplated to be within the scope of the present invention.

The present invention further provides novel compounds of Formula (I), represented by Formula (Ia) :



wherein:

A represents hydroxy;

D represents aryl or heteroaryl;

E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

$R^2$  and  $R^3$  are independently selected from hydrogen,  $C_{1-6}$ alkyl, aryl and heteroaryl; or  $R^2$  and  $R^3$  together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

- 5  $R^4$  is selected from the group consisting of  $C_{1-6}$ alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

- $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen,  $C_{1-6}$ alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or  $R^5$  and  $R^6$  together with the nitrogen atom to  
10 which they are attached form a 5 or 6 membered saturated cyclic group; and

J represents  $C_{1-6}$ alkyl, heterocyclalkyl, arylalkyl or heteroarylalkyl;

- provided that i) E and G are not both hydrogen; and  
15 ii) the compound is other than  
4-ethenyl-1-(2-nitrobenzoyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;  
1-(2-aminobenzoyl)-4-(1-hydroxyethyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;  
4-(1-hydroxyethyl)-1-(2-nitrobenzoyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;

- 20 and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl.

- Preferably, D represents phenyl, more preferably *tert*-butylphenyl, especially preferred is  
25 *para-tert*-butylphenyl optionally further *meta*-substituted by halo,  $C_{1-3}$ alkyl or  $C_{1-3}$ alkoxy.

Preferably, E is selected from the group consisting of  $C_{1-6}$ alkyl, aryl and heteroaryl; more preferably E represents heteroaryl.

- 30 Preferably, G is  $C_{1-6}$ alkyl optionally substituted by halo,  $OR^1$ ,  $SR^1$ , and cyano.

Preferably, J is  $C_{1-6}$ alkyl, arylalkyl or heteroarylalkyl; more preferably J is isobutyl, benzyl or pyridyl.

- 35 In one aspect of the present invention, when D is phenyl substituted by at least two substituents independently selected from hydroxy, alkoxy,  $-CO_2H$ ,  $-CO_2R^4$ , or fluoro; G is hydrogen or  $C_{1-6}$ alkyl; and J is  $C_{1-6}$ alkyl; then E is aryl, heteroaryl or heterocycl.

- 40 As used herein unless otherwise specified, "alkyl" refers to an optionally substituted hydrocarbon group. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Where the alkyl hydrocarbon group is cyclic, it will be understood that there will be a minimum of 3 carbon atoms in the group. Preferably, the group is

saturated. Preferred alkyl moieties are C<sub>1-4</sub>alkyl. Unless otherwise stated, optional substituents include C<sub>1-6</sub>alkyl, halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>H, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano, oxo, and heterocyclyl.

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As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. "Aryl" includes carbocyclic aryl and biaryl groups, all of which may be optionally substituted. Preferred "aryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted phenyl. Preferred "aryl" substituents are selected from the group consisting of C<sub>1-6</sub>alkyl, halo, OR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>H, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano, oxo, heterocyclyl, CF<sub>3</sub>, and NO<sub>2</sub>.

10

As used herein, "heteroaryl" refers to an optionally substituted, 5 or 6 membered, aromatic group comprising one to four heteroatoms selected from N, O and S, with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Preferred "heteroaryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted pyridyl and thiazolyl. Preferred "heteroaryl" substituents are selected from the group consisting of C<sub>1-6</sub>alkyl, halo, OR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>H, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano, oxo, heterocyclyl, CF<sub>3</sub>, and NO<sub>2</sub>.

15

20

As used herein, "heterocyclic" and "heterocyclyl" refer to an optionally substituted, 5 or 6 membered, saturated cyclic hydrocarbon group containing 1 or 2 heteroatoms selected from N, optionally substituted by hydrogen, C<sub>1-6</sub>alkyl, C(O)R<sup>4</sup>, SO<sub>2</sub>R<sup>4</sup>, aryl or heteroaryl; O; and S, optionally substituted by one or two oxygen atoms.

25

Preferred compounds of Formula (I) useful in the present invention are selected from the group consisting of:

30

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid ;

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-fluoromethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

35

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

2-Allyl-1-(3-bromo-4-*tert*-butylbenzoyl)-pyrrolidine-2-carboxylic acid;

2-Benzyl-1-(3-bromo-4-*tert*-butylbenzoyl)-pyrrolidine-2-carboxylic acid;

40

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

- rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-allyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
5 *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-propyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-  
10 2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropenyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid; and  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
15 and salts, solvates and esters, and individual enantiomers thereof.

Preferred compounds of Formula (Ia) are selected from the group consisting of:

- rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-  
20 2-yl)pyrrolidine-2-carboxylic acid ;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-fluoromethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
25 *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
30 *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-allyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-propyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
35 *rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropenyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid; and

- 5 *rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

and salts, solvates and esters, and individual enantiomers thereof.

- 10 Also included in the present invention are pharmaceutically acceptable salt complexes. The present invention also covers the physiologically acceptable salts of the compounds of formula (I). Suitable physiologically acceptable salts of the compounds of formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for  
15 example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

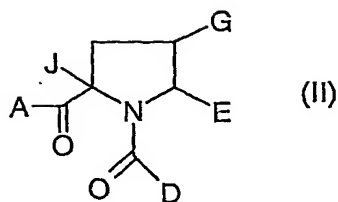
- 20 The present invention also relates to solvates of the compounds of Formula (I), for example hydrates.

- The present invention also relates to pharmaceutically acceptable esters of the compounds of Formula (I) and (Ia), for example carboxylic acid esters -COOR, in which R is selected from  
25 straight or branched chain alkyl, for example n-propyl, n-butyl, alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl optionally substituted by halogen, C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy or amino). Unless otherwise specified, any alkyl moiety present in such esters preferably contains 1 to 18 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters preferably comprises  
30 a phenyl group.

It will further be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

35

Compounds of Formula (I) and (Ia) in which A is hydroxy may be prepared from a compound of Formula (II)



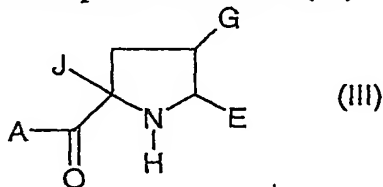
in which A is an alkoxy, benzyloxy or silyloxy group. For example when A is *tert*-butoxy, and D, E, G and J are as defined above for Formula (I), by treatment with an appropriate acid, for example trifluoroacetic acid. Suitably, the reaction is carried out in a solvent, for example dichloromethane. Preferably, the temperature is in the range 0 to 50°C, more preferably 20 to 30°C.

For example when A is benzyloxy, and D, E, G and J are as defined above for Formula (I), by hydrogenolysis in the presence of a suitable catalyst for example palladium-on-carbon. Suitably, the reaction is carried out in a solvent, for example ethanol. Preferably, the temperature is in the range 0 to 50°C.

For example when A is allyloxy, and D, E, G and J are as defined above for Formula (I), by treatment with a suitable catalyst for example tetrakis(triphenylphosphine)palladium(0) and a suitable proton source, for example phenylsilane. The reaction is carried out in a suitable solvent, for example dichloromethane.

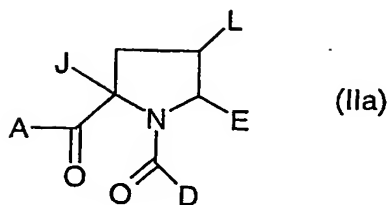
For example when A is silyloxy, and D, E, G and J are as defined above for Formula (I), by treatment with a suitable fluoride source for example tetrabutylammonium fluoride. The reaction is carried out in a suitable solvent, for example tetrahydrofuran.

Compounds of Formula (I) and (Ia) in which A is hydroxy or a protected form thereof may also be prepared by reaction of a compound of Formula (III)



in which A, E, G, and J are as defined above for Formula (I); with a suitable acylating agent, for example D-C(O)-hal, wherein hal is a halo atom, preferably chloro or bromo, and D is as defined above for Formula (I). Preferably the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine and thereafter removing any protecting group. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3<sup>rd</sup> Ed (1999), J Wiley and Sons

Compounds of Formula (II) in which G represents optionally substituted alkyl, for example hydroxyalkyl, may be prepared by appropriate manipulation of a compound of Formula (IIa)



in which L represents  $\text{CO}_2\text{Y}$  or  $\text{COY}$  wherein Y represents hydrogen or alkyl. For example, a compound of Formula (II) in which G represents hydroxyalkyl may be prepared by reduction of a compound of Formula (IIa) in which L represents  $\text{CO}_2\text{Y}$  or  $\text{COY}$  and Y represents alkyl, using a suitable reducing agent, for example lithium borohydride or sodium borohydride, in a suitable solvent for example tetrahydrofuran.

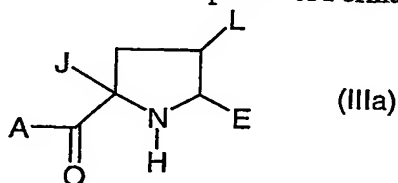
In a further aspect, a compound of Formula (II) in which G represents hydroxyalkyl may be converted into a compound of Formula (II) in which G represents optionally substituted alkyl, for example alkyl, haloalkyl or alkoxyalkyl. For example, a compound of Formula (II) in which G represents alkoxyalkyl may be prepared by alkylation of a compound of formula (II) in which G represents hydroxyalkyl using a suitable base for example sodium hydride and a suitable alkylating agent for example methyl iodide or ethyl iodide. Preferably the reaction is carried out in a suitable solvent, for example dimethylformamide.

For example, a compound of Formula (II) in which G represents haloalkyl may be prepared by halogenation of a compound of Formula (II) in which G represents hydroxyalkyl using a suitable halogenating agent, for example fluoromethyl may be prepared using diethylaminosulfur trifluoride, in a suitable solvent, for example dichloromethane.

For example, a compound of Formula (II) in which G represents methyl may be prepared by deoxygenation of a compound of formula (II) in which G represents hydroxymethyl. The deoxygenation is suitably carried out in a two step process in which:

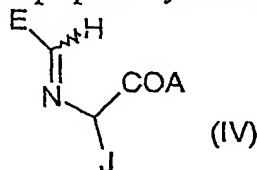
Step(i) A compound of formula (II) in which G represents hydroxymethyl is converted into a thionocarbonate by treatment with a suitable chloroformate for example 4-fluorophenyl thionochloroformate. Preferably the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base catalyst, for example N,N-dimethyl-4-aminopyridine. Step(ii) The thionocarbonate from step(i) is treated with a suitable radical initiator, for example AIBN, and a suitable proton source, such as tris(trimethylsilyl)silane, in a suitable solvent, for example dioxan. Preferably, the temperature is in the range 80 to  $120^\circ\text{C}$ .

A compound of Formula (IIa) in which L represents  $\text{CO}_2\text{Y}$  or  $\text{COY}$  wherein Y represents hydrogen or alkyl may be prepared from a compound of Formula (IIIa)

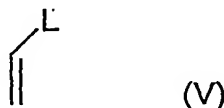


in which L represents  $\text{CO}_2\text{Y}$  or  $\text{COY}$  wherein Y represents hydrogen or alkyl, and A, E, and J are as defined above for Formula (I); with a suitable acylating agent, for example  $\text{D-C(O)-hal}$ , wherein hal is a halo atom, preferably chloro or bromo, and D is as defined above for Formula (I). Preferably the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example triethylamine.

A compound of Formula (IIIa) may be prepared by reaction of a compound of Formula (IV)



in which E and J are as defined above for Formula (I) and A is as defined above for Formula (II) with a compound of Formula (V)

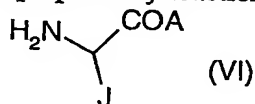


wherein L represents  $\text{CO}_2\text{Y}$  or  $\text{COY}$  wherein Y represents hydrogen or alkyl. Preferably, the reaction is carried out in a suitable solvent, for example THF or acetonitrile, optionally in the presence of a Lewis acid catalyst, such as lithium bromide or silver acetate, and a base, such as triethylamine, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) or tetramethyl guanidine. Alternatively, the reaction is carried out in a suitable solvent, for example THF or acetonitrile, in the presence of an acid, such as acetic acid, or the reaction may be carried out by heating compounds of Formula (IV) and Formula (V) in a suitable solvent, for example toluene, xylene or acetonitrile in the absence of a catalyst.

Compounds of Formula (III) in which G represents optionally substituted alkyl, for example hydroxyalkyl, may be prepared by appropriate manipulation of a compound of Formula (IIIa) after first protecting the N-atom of the pyrrolidine ring with a suitable N-protecting group, for example benzyloxycarbonyl (CBZ). For example, a compound of Formula (III) in which G represents hydroxyalkyl may be prepared by reduction of a compound of Formula (IIIa) in which L represents  $\text{CO}_2\text{Y}$  and Y represents alkyl, using a suitable reducing agent, for example lithium borohydride or sodium borohydride, in a suitable solvent for example tetrahydrofuran. Deprotection of the N-atom by standard procedures results in the compound of Formula (III). For example, when the N-protecting group is CBZ, deprotection may be achieved by catalytic hydrogenolysis.

In a similar manner to that described above in relation to compounds of Formula (II), a compound of Formula (III), in which G represents hydroxyalkyl and the N-atom is protected, may be converted into a compound of Formula (III) in which G represents optionally substituted alkyl, for example alkyl, haloalkyl or alkoxyalkyl and the N-atom is protected. Deprotection of the N-atom by standard procedures results in the compound of Formula (III).

Compounds of Formula (IV) May be prepared by reaction of a compound of Formula (VI)



in which J is as defined above for Formula (I) and A is as defined above for Formula (II) with a compound of Formula E-CHO in the presence of a suitable base, for example triethylamine, in a suitable solvent, for example dichloromethane.

Compounds of Formula (VI) and E-CHO are known in the art or may be prepared by standard literature procedures.

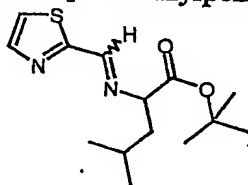
Compounds of Formula (I) in which A is an ester may be prepared by esterification of a compound of Formula (I) in which A is hydroxy by standard literature procedures for esterification.

With appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3<sup>rd</sup> Ed (1999), J Wiley and Sons.

### EXAMPLES

#### Intermediate 1

2-[N-(1,3-Thiazol-2-ylmethylene)amino]-4-methylpentanoic acid, *tert*-butyl ester

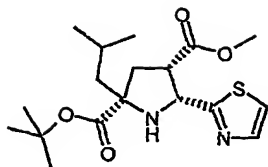


A stirred mixture of 2-amino-4-methyl-pentanoic acid *tert*-butyl ester, hydrochloride salt (5.00g, 22.34 mmol), 1,3-thiazole-2-carboxaldehyde (2.53g, 22.34 mmol) and triethylamine (3.10 mL, 22.3 mmol) in dichloromethane (60 mL) was heated under reflux under nitrogen for 19 hours. The reaction mixture was allowed to cool to room temperature, washed twice with water, dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the title compound as an oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.46 (s, 1H), 7.94 (d, 1H), 7.44 (dd, 1H), 4.07 (dd, 1H), 1.89-1.74 (m, 2H), 1.64-1.52 (m, 1H), 1.48 (s, 9H), 0.96 (d, 3H) and 0.90 (d, 3H).

#### Intermediate 2

*rel*-(2S,4S,5R)-2-Isobutyl-5-(1,3-thiazol-2-yl)pyrrolidine-2,4-dicarboxylic acid, 2-*tert*-butyl ester, 4-methyl ester

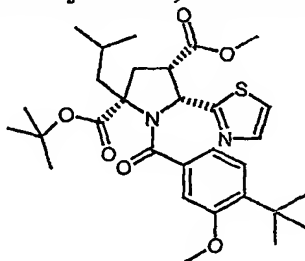


Racemic;  
Relative stereochemistry shown

- To a cooled (0°C) stirred solution of Intermediate 1 (0.53 g, 1.88 mmol) in anhydrous THF (3 mL) under nitrogen, was added methyl acrylate (254 uL, 2.83 mmol) followed by lithium bromide (0.33 g, 3.80 mmol) and triethylamine (390 uL, 2.82 mmol). The reaction was stirred in a cooling bath for 5 min. and then at ambient temperature overnight. Aqueous ammonium chloride (15 mL) was added and the resulting mixture was extracted with ethyl acetate (20 mL). The extracts were combined and washed with water and brine then dried (MgSO<sub>4</sub>). The solvent was evaporated *in vacuo* to give the title compound as a solid.
- MS calcd for (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S + H)<sup>+</sup>: 369
- MS found (electrospray): (M+H)<sup>+</sup> = 369.

### Intermediate 3

*rel*-(2*S*,4*S*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-5-(1,3-thiazol-2-yl)-pyrrolidine-2,4-dicarboxylic acid, 2-*tert*-butyl ester, 4-methyl ester



Racemic;  
Relative stereochemistry shown

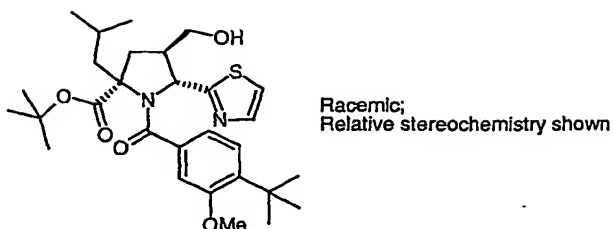
- To a stirred solution of 3-methoxy-4-*tert*-butylbenzoyl chloride<sup>1</sup> (3.36 g, 37 mmol) in anhydrous dichloromethane (50 mL) was added Intermediate 2 (4 g, 24 mmol) and triethylamine (2.27 mL, 37 mmol). This mixture was stirred for 6 hours under nitrogen and was then diluted with dichloromethane and washed with water. The organic phase was dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The residue was purified by crystallisation from dichloromethane and washing with diethyl ether to provide the title compound as a solid.
- MS calcd for (C<sub>30</sub>H<sub>42</sub>N<sub>2</sub>O<sub>6</sub>S + H)<sup>+</sup>: 559
- MS found (electrospray): (M+H)<sup>+</sup> = 559.

- Ref.
- (1) Synthesised from 3-methoxy-4-*tert*-butylbenzoic acid (*J.Org.Chem.*, 26, 1961,1732-1737).

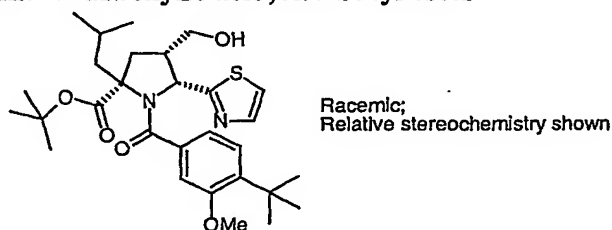
### Intermediate 4 and Intermediate 4a

#### Intermediate 4

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester

**Intermediate 4a**

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



To a stirred solution of Intermediate 3 (2.3 g, 4.12 mmol) in anhydrous THF (23 mL) at room temperature under nitrogen, was added a 2M solution of lithium borohydride in THF (2.93 mL, 5.85 mmol). This solution was stirred at room temperature overnight and was then quenched with 1M K<sub>2</sub>CO<sub>3</sub> solution (100 mL) and extracted with ethyl acetate (100 mL, then 50 mL). The combined organic phases were dried (MgSO<sub>4</sub>) and evaporated *in vacuo*. The resulting gum was purified by chromatography on silica gel using cyclohexane-ethyl acetate (7:3 v/v) as eluent to give **Intermediate 4a**, *rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert* butyl ester followed by **Intermediate 4**, *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester.

**Intermediate 4**

MS calcd for (C<sub>29</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 531

MS found (electrospray): (M+H)<sup>+</sup> = 531.

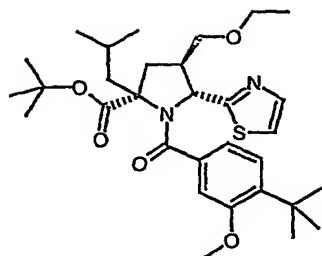
**Intermediate 4a**

MS calcd for (C<sub>29</sub>H<sub>42</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 531

MS found (electrospray): (M+H)<sup>+</sup> = 531

**Intermediate 5**

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Racemic;  
Relative stereochemistry shown

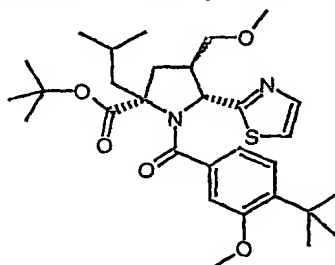
To a solution of Intermediate 4 (0.14 g) in anhydrous DMF (5 mL) was added sodium hydride (60% dispersion in mineral oil, 16 mg). When gas evolution had subsided iodoethane (0.084 mL) was added. The mixture was stirred at ambient temperature under an atmosphere of nitrogen for 18 h. Further quantities of sodium hydride dispersion (17 mg) and iodoethane (0.084 mL) were added and the mixture was stirred for a further 24h. Methanol (10 mL) was added and the mixture was stirred for 10 min. Volatiles were removed and the residue was dissolved in ethyl acetate (15 mL), washed with water (15 mL) and then dried (MgSO<sub>4</sub>). Removal of solvent gave the crude product which was purified by silica gel chromatography eluting with 5:1 (v/v) cyclohexane/ethyl acetate) to give the title compound as an oil.

MS calcd for (C<sub>31</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 559

MS found (electrospray): (M+H)<sup>+</sup> = 559

#### 15 Intermediate 6

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Racemic;  
Relative stereochemistry shown

The title compound was prepared from Intermediate 4 in a similar manner to Intermediate 5.

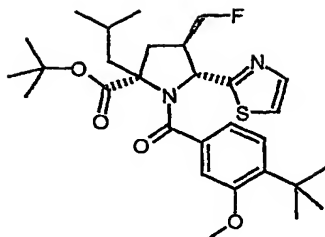
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MS calcd for (C<sub>30</sub>H<sub>44</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 545

MS found (electrospray): (M+H)<sup>+</sup> = 545

#### 25 Intermediate 7

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-fluoromethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Racemic;  
Relative stereochemistry shown

To a solution of Intermediate 4 (0.147 g) in anhydrous dichloromethane (3 mL) at 0°C was added diethylamino sulfur trifluoride (0.073 mL). The cooling bath was removed and the mixture was stirred at ambient temperature for 3h. The mixture was cooled to 0°C and poured into pre-cooled saturated sodium hydrogen carbonate solution (10 mL) and then extracted with dichloromethane (2 x 20 mL). The extracts were combined, washed with brine and dried (MgSO<sub>4</sub>). Solvent was removed and the residue was purified by silica gel chromatography eluting with 3:1 (v/v) cyclohexane/ethyl acetate to give the title compound as a gum.

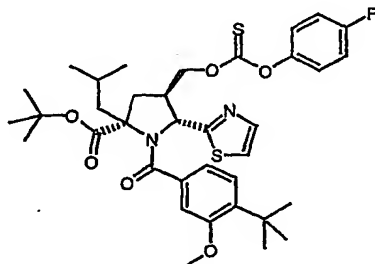
MS calcd for ((C<sub>29</sub>H<sub>41</sub>FN<sub>2</sub>O<sub>4</sub>S + H)<sup>+</sup> : 533

MS found (electrospray): (M+H)<sup>+</sup> = 533

#### Intermediate 8

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-(4-

fluorophenoxythiocarbonyloxymethyl)-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid ,  
2-*tert*-butyl ester



Racemic;  
Relative stereochemistry shown

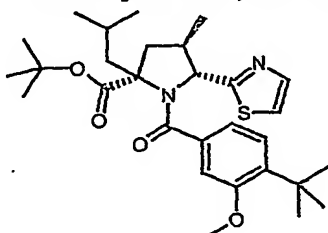
To a solution of Intermediate 4 (0.31 g) in anhydrous dichloromethane (5 mL) was added 4-fluorophenyl thionochloroformate (0.125 mL) followed by 4-dimethylaminopyridine (214 mg). The resulting solution was stored at ambient temperature for 2 days, diluted to 50 mL with dichloromethane and washed successively with 25 mL portions of 0.5M hydrochloric acid, water and saturated brine, and then dried (MgSO<sub>4</sub>). Solvent was removed and the residue was purified by silica gel chromatography eluting with 3:1 v/v cyclohexane/ethyl acetate to give the title compound as a foam.

MS calcd for (C<sub>36</sub>H<sub>45</sub>N<sub>2</sub>O<sub>6</sub>S<sub>2</sub> + H)<sup>+</sup> : 685

MS found (electrospray): (M + H)<sup>+</sup> = 685

#### Intermediate 9

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



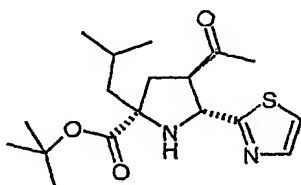
Racemic;  
Relative stereochemistry shown

To a solution of Intermediate 8 (0.30g) in dioxan (4 mL) was added 2,2'-azobis-isobutyronitrile (AIBN) (31 mg) followed by tris(trimethylsilyl)silane (0.183 mL). The mixture was heated under reflux for 30 min and set aside to cool to ambient temperature overnight. Volatiles were removed and the residue was purified by silica gel chromatography eluting with 6:1 (v/v) cyclohexane/ethyl acetate to give the title compound as a solid.

MS calcd for (C<sub>29</sub>H<sub>42</sub>N<sub>2</sub>O<sub>4</sub>S + H)<sup>+</sup>: 515  
MS found (electrospray): (M + H)<sup>+</sup> = 515

#### Intermediate 10

*rel*-(2S,4R,5R)-2-Isobutyl-4-acetyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



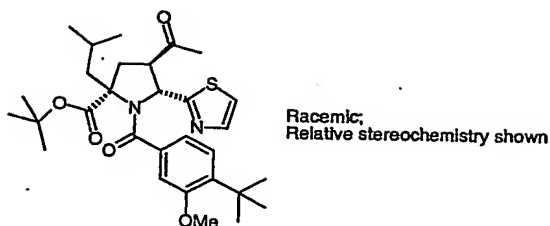
Racemic;  
Relative stereochemistry shown

To a cooled (0°C) stirred solution of Intermediate 1 (3.00 g, 10.6 mmol) in anhydrous THF (25 mL) under nitrogen, was added methyl vinyl ketone (1.0 mL, 11.7 mmol) followed by lithium bromide (1.75 g, 20.1 mmol) and triethylamine (2.2 mL, 15.9 mmol). The reaction was stirred in a cooling bath for 10 min. and then at ambient temperature overnight. The reaction mixture was diluted with ethyl acetate (80 mL) and saturated ammonium chloride solution (40 mL). The two phases were separated and the aqueous phase was re-extracted with ethyl acetate (80 mL). The extracts were combined and washed with brine then dried (MgSO<sub>4</sub>). The solvent was evaporated *in vacuo* to give the crude product. This was purified by chromatography on silica gel using a cyclohexane-ethyl acetate gradient (95:5 v/v to 9:1 v/v) as eluent to provide the title compound as an oil.

MS calcd for (C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S + H)<sup>+</sup>: 353.  
MS found (electrospray): (M+H)<sup>+</sup> = 353.

#### Intermediate 11

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-acetyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester

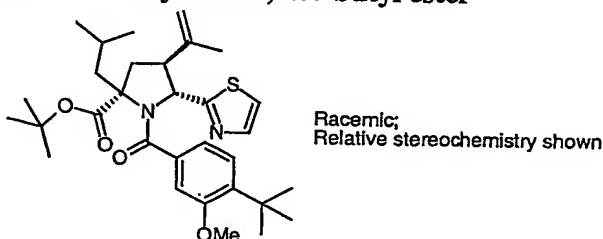


To a stirred solution of 3-methoxy-4-*tert*-butylbenzoyl chloride (0.32g, 1.41 mmol) in anhydrous dichloromethane (5 mL) at 0°C was added Intermediate 10 (0.45g, 1.28 mmol) and triethylamine (196  $\mu$ L, 1.41 mmol). This mixture was stirred for 16 hours and was then diluted with dichloromethane (40 mL) and washed with water (40 mL). The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo*. The residue was purified by chromatography on silica gel using a cyclohexane-ethyl acetate gradient (95:5 v/v to 85:15 v/v) as eluent to provide the title compound as a solid.

- 10 MS calcd for  $(\text{C}_{30}\text{H}_{42}\text{N}_2\text{O}_5\text{S} + \text{H})^+$ : 543.  
MS found (electrospray):  $(\text{M}+\text{H})^+ = 543$ .

#### Intermediate 12

*rel*-(2*S*,4*S*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropenyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



To a suspension of methyltriphenylphosphonium bromide (0.295 g, 0.83 mmol) in anhydrous THF (3 mL) at 0°C under nitrogen, was added, slowly, a 1.0M solution of lithium bis(trimethylsilyl)amide in THF (0.83 mL, 0.83 mmol). The bright yellow solution was stirred at 0°C for 15 min. before addition of Intermediate 11 (0.32 g, 0.59 mmol) as a solution in anhydrous THF (4 mL). The reaction was stirred at 0°C for 1 hour and was then left to warm to room temperature and stir overnight. The reaction mixture was diluted with sat. ammonium chloride solution (40 mL) and ethyl acetate (40 mL). The organic phase was then washed with water (40 mL) and brine (40 mL), dried ( $\text{MgSO}_4$ ) and the solvent evaporated *in vacuo*.

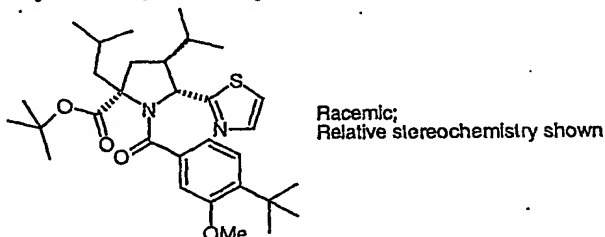
The residue was purified by chromatography on silica gel using cyclohexane-ethyl acetate (95:5 v/v) as eluent to provide the title compound as a foam.

MS calcd for  $(\text{C}_{31}\text{H}_{44}\text{N}_2\text{O}_4\text{S} + \text{H})^+$ : 541.

MS found (electrospray):  $(\text{M}+\text{H})^+ = 541$ .

#### Intermediate 13

*rel*-(2*S*,4*S*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Intermediate 12 (0.164g, 0.3 mmol) in ethanol (15 mL) was hydrogenated over 10% palladium on carbon (38 mg) for six hours. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to give the title compound as a foam.

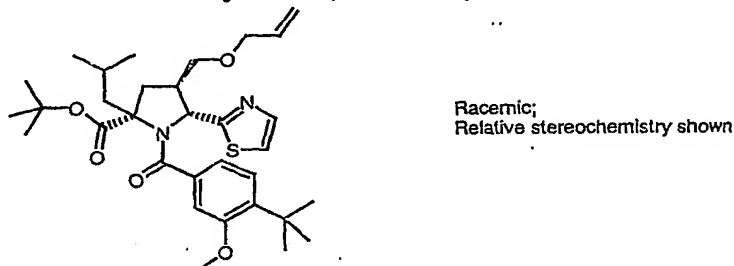
MS calcd for (C<sub>31</sub>H<sub>46</sub>N<sub>2</sub>O<sub>4</sub>S + H)<sup>+</sup>: 543.

MS found (electrospray): (M+H)<sup>+</sup> = 543.

10

#### Intermediate 14

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-allyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, 2-*tert*-butyl ester



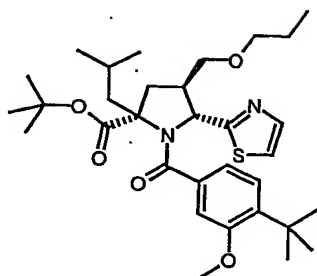
To a solution of Intermediate 4 (0.200 g) in anhydrous DMF (5 mL) was added sodium hydride (60% dispersion in mineral oil, 24 mg). When gas evolution had subsided allyl iodide (0.139 mL) was added. The mixture was stirred at ambient temperature under an atmosphere of nitrogen for 23 h. Methanol (10 mL) was added and the mixture was stirred for 10 min. Volatiles were removed and the residue was dissolved in ethyl acetate (15 mL), washed with water (15 mL), then brine (15 mL) and then dried (MgSO<sub>4</sub>). Removal of solvent gave the crude product which was purified by silica gel chromatography eluting with 5:1 (v/v) cyclohexane/ethyl acetate to give the title compound as a gum.

MS calcd for (C<sub>32</sub>H<sub>46</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 571

MS found (electrospray): (M+H)<sup>+</sup> = 571.

#### Intermediate 15

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-propyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, 2-*tert*-butyl ester



Racemic;  
Relative stereochemistry shown

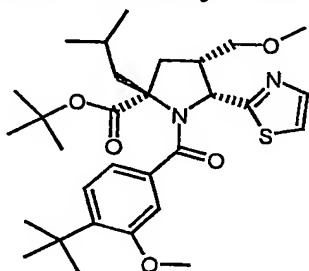
A solution of Intermediate 14 (0.03 g) in ethanol (5 mL) was added to 10% palladium on carbon (0.10 g) and the resulting mixture was stirred in an atmosphere of hydrogen for 4.5 h. A further quantity of 10% palladium on carbon (0.01 g) was added and the mixture was stirred in an atmosphere of hydrogen for a further 18 h. Catalyst was removed by filtration and washed with ethanol. The filtrate and washings were combined and evaporated to dryness to give the title compound as a gum.

MS calcd for  $(C_{32}H_{48}N_2O_5S + H^+)$ : 573

MS found (electrospray):  $(M+H)^+ = 573$ .

#### Intermediate 16

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Racemic;  
Relative stereochemistry shown

To a stirred solution of intermediate 4a (100 mg, 0.2 mmol) in anhydrous DMF (5mL) was added sodium hydride (60% in mineral oil, 8mg, 0.2 mmol) under nitrogen and at  $-15^{\circ}\text{C}$ . The slurry is stirred at  $-15^{\circ}\text{C}$ . over 30 min, then methyl iodide (0.25 mL, 0.4 mmol, 2 eq) was added and the reaction is stirred at  $-15^{\circ}\text{C}$  to room temp over 18 hours.

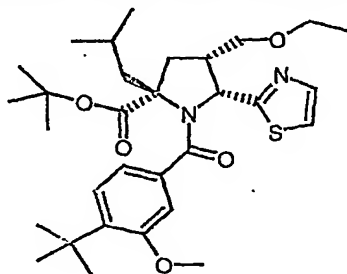
Methanol (10 mL) was added and reaction stirred for 15 min. The solvent was evaporated and the residue partitioned between water and ethyl acetate. The organic layer was dried with  $\text{NaSO}_4$  and evaporated to give a yellow oil. The oil was purified by chromatography on silica gel using cyclohexane-ethyl acetate (2:3 v/v) as eluent to provide the title compound as a solid.

MS calcd for  $(C_{30}H_{44}N_2O_5S + H^+)$ : 545.

MS found (electrospray):  $(M+H)^+ = 545$

#### Intermediate 17

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid, *tert*-butyl ester



Racemic;  
Relative stereochemistry shown

The title compound was prepared in a similar manner to Intermediate 16 from Intermediate 4a

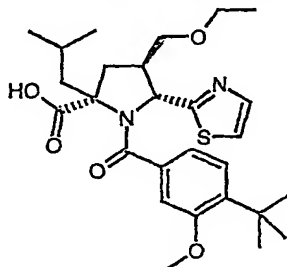
5

MS calcd for  $(C_{31}H_{46}N_2O_5S + H)^+$ : 559

MS Found (electrospray):  $(M+H)^+ = 559$ .

#### Example 1

10 *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

To a solution of Intermediate 5 (0.053 g) in anhydrous dichloromethane (1 mL) was added trifluoroacetic acid (1 mL). The mixture was stored at 20°C temperature overnight. The mixture was evaporated and the residue was triturated with ether to give the title compound as a solid.

15

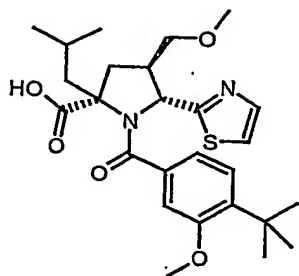
MS calcd for  $(C_{27}H_{38}N_2O_5S + H)^+$ : 503

MS found (electrospray):  $(M+H)^+ = 503$

20

#### Example 2

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

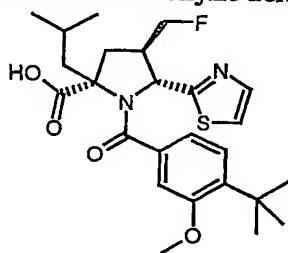
The title compound was prepared in a similar manner to Example 1 from Intermediate 6.

MS calcd for  $(C_{26}H_{36}N_2O_5S + H)^+$  : 489

5 MS found (electrospray):  $(M+H)^+ = 489$

### Example 3

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-fluoromethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

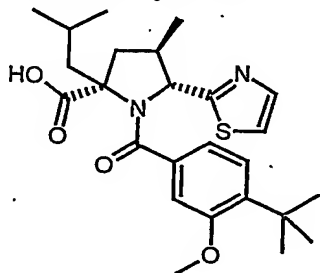
10 The title compound was prepared in a similar manner to Example 1 from Intermediate 7.

MS calcd for  $(C_{25}H_{33}FN_2O_4S + H)^+$  : 477

15 MS found (electrospray):  $(M+H)^+ = 477$

### Example 4

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

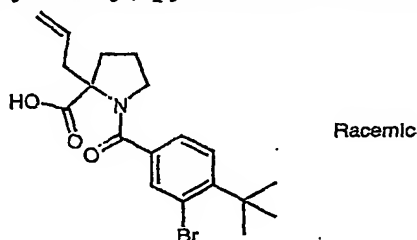
20 The title compound was prepared in a similar manner to Example 1 from Intermediate 9.

MS calcd for  $(C_{25}H_{34}N_2O_4S + H)^+$  : 459

MS found (electrospray):  $(M+H)^+$  = 459

### Example 5

#### 5 2-allyl-1-(3-bromo-4-*tert*-butylbenzoyl)-pyrrolidine-2-carboxylic acid



- 2-Allyl-pyrrolidine-2-carboxylic acid hydrochloride (*J. Chem. Soc. Chem. Commun.*, 1988, 22, 1447) (64 mg) was dissolved in dichloromethane (5 mL) and treated with 3-bromo-4-*tert*-butylbenzoyl chloride<sup>1</sup> (101 mg) and triethylamine (139  $\mu$ L). The mixture was stirred at room temperature for 18 h. Hydrochloric acid (2N, 5 mL) was added and the mixture stirred for 5 min. The organic was separated using a PTFE filter and concentrated to give a yellow gum. This was purified by reverse phase HPLC on a  $C_{18}$  column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents, and analysis of the fractions by electrospray mass spectroscopy, to give the title compound as a solid (68 mg)

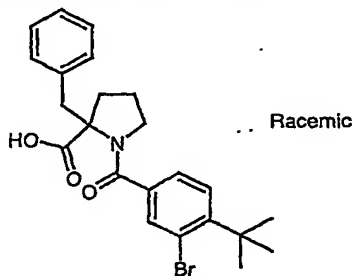
MS calcd for  $(C_{19}H_{24}BrNO_3 + H)^+$  : 394/396

MS found (electrospray):  $(M+H)^+$  = 394/396

- (1) Synthesised from 3-bromo-4-*tert*-butylbenzoic acid (*Aust. J. Chem.*, 1990, 43, 807).

### Example 6

#### 2-benzyl-1-(3-bromo-4-*tert*-butylbenzoyl)-pyrrolidine-2-carboxylic acid



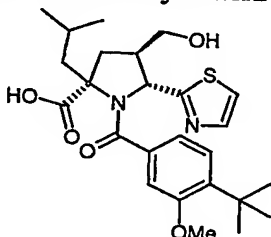
- The title compound was prepared in a similar manner to Example 5 from 2-benzyl-pyrrolidine-2-carboxylic acid.

MS calcd for  $(C_{23}H_{26}BrNO_3 + H)^+$  : 444/446

MS found (electrospray):  $(M+H)^+$  = 444/446

**Example 7**

*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



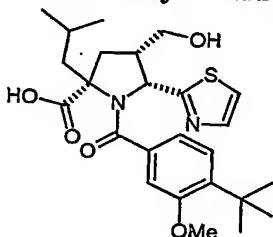
Racemic;  
Relative stereochemistry shown

- 5 To a solution of Intermediate 4 (52 mg, 0.098 mmol), was added trifluoroacetic acid (2 mL). The solution was left overnight at room temperature. The solvent was evaporated in vacuo and the residue was co-evaporated with CH<sub>2</sub>Cl<sub>2</sub> (x2) and toluene, then triturated with diethyl ether. The resulting white solid was treated with 1 mL of a solution of NaOH in methanol (6.4 mg NaOH in 1mL MeOH) and was stirred at room temperature overnight. The solvent
- 10 was then evaporated *in vacuo* and the residue was purified by reverse phase HPLC on a C<sub>18</sub> column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents to give the title compound as a solid.

- 15 MS calcd for (C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 475  
MS found (electrospray): (M+H)<sup>+</sup> = 475

**Example 8**

- 20 *rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



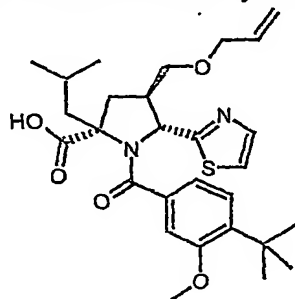
Racemic;  
Relative stereochemistry shown

The title compound was prepared in a similar manner to Example 7 from Intermediate 4a.

- MS calcd for (C<sub>25</sub>H<sub>34</sub>N<sub>2</sub>O<sub>5</sub>S + H)<sup>+</sup>: 475
- 25 MS found (electrospray): (M+H)<sup>+</sup> = 475

**Example 9**

*rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-allyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

The title compound was prepared in a similar manner to Example 1 from Intermediate 14.

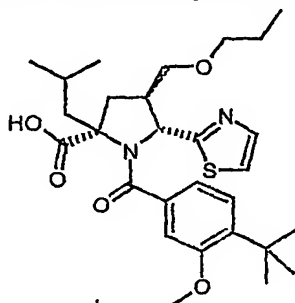
5

MS calcd for (C<sub>28</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub>S+ H<sup>+</sup>) : 515

MS found (electrospray): (M+H)<sup>+</sup> = 515

#### Example 10

10 *rel*-(2*S*,4*R*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-propyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

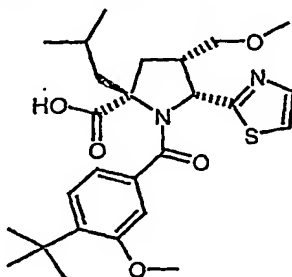
The title compound was prepared in a similar manner to Example 1 from Intermediate 15.

15 MS calcd for (C<sub>28</sub>H<sub>40</sub>N<sub>2</sub>O<sub>5</sub>S+ H<sup>+</sup>) : 517

MS found (electrospray): (M+H)<sup>+</sup> = 517

#### Example 11

20 *rel*-(2*S*,4*S*,5*R*)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



Racemic;  
Relative stereochemistry shown

To a solution of Intermediate 16 (51 mg, 0.1 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (2 mL) and the solution stirred at ambient temperature overnight. The

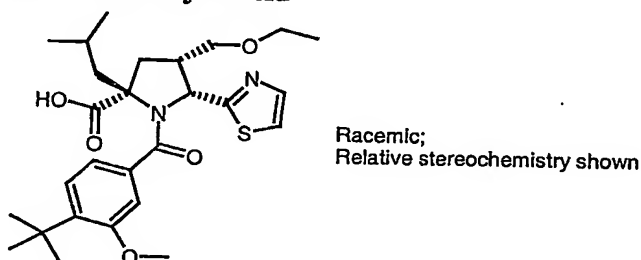
reaction mixture was evaporated and the residue triturated with diethylether to give the title compound as a solid.

MS calcd for  $(C_{26}H_{36}N_2O_5S + H)^+$ : 489.

5 MS found (electrospray):  $(M+H)^+ = 489$

**Example 12**

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



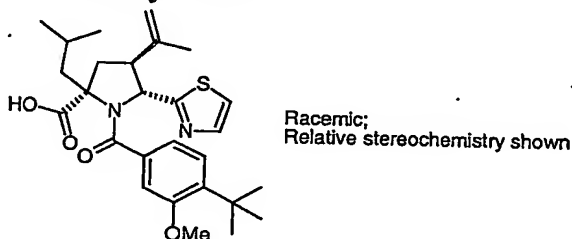
10 The title compound was prepared in a similar manner to Example 11 from Intermediate 17

MS calcd for  $(C_{27}H_{38}N_2O_5S + H)^+$ : 502

MS found (electrospray):  $(M+H)^+ = 502$ .

**Example 13**

*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropenyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



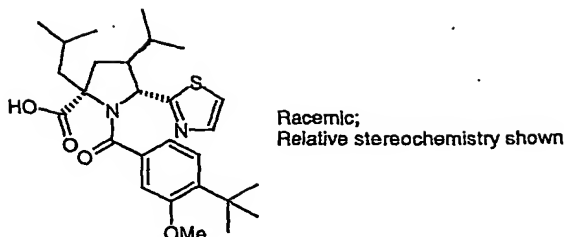
20 Intermediate 12 (74 mg, 0.14 mmol) was dissolved in trifluoroacetic acid (2 mL). The reaction was left at room temperature overnight. The solvent was then evaporated *in vacuo* and the residue was triturated with diethyl ether. The resulting solid was collected by filtration and dried *in vacuo* to give the title compound.

25 MS calcd for  $(C_{27}H_{36}N_2O_4S + H)^+$ : 485.

MS found (electrospray):  $(M+H)^+ = 485$ .

**Example 14**

30 *rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid



The title compound was prepared in a similar manner to Example 1 from Intermediate 13.

MS calcd for  $(C_{27}H_{38}N_2O_4S + H)^+$ : 487.

5 MS found (electrospray):  $(M+H)^+ = 487$ .

10 The compounds according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in admixture with one or more physiologically acceptable diluents or carriers.

15 The compounds of the present invention can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

20 Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the  
25 the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

30 Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

35 For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various compounds to be administered can be determined by standard procedures taking into account factors such as the compound ( $IC_{50}$ ) potency, ( $EC_{50}$ ) efficacy, and the biological half-life (of the compound), the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a preferred method of administration of the present compounds.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

Composition of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

5

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

10

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

15

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

#### ASSAYS

20

The potential for compounds of the invention to inhibit NS5B wildtype HCV polymerase activity may be demonstrated, for example, using one of the following *in vitro* assays:

##### In Vitro Detection of inhibitors of HCV RNA-dependent RNA Polymerase Activity (A)

25

Incorporation of [<sup>3</sup>H]-UMP into RNA was followed by absorption of the RNA polymer onto a DEAE glass fibre filter. A synthetic template consisting of 16mer oligoU hybridised to polyrA (10:1 w/w) was used as a homopolymer substrate.

30

Reaction Conditions were 22 µM [<sup>3</sup>H]-UTP (0.75 Ci/mMol), 1 mM-Dithiothreitol, 3.2 mM-MgCl<sub>2</sub>, 20 mM-Tris-HCl, pH7.0, 10 µg/mL polyA-oligoU, and 90 mM-NaCl. Note that 50mM-NaCl is added with the enzyme.

35

HCV RNA Polymerase (Recombinant full-length NS5B (Lohmann et al, J. Virol. 71 (11), 1997, 8416 'Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity') expressed in baculovirus and purified to homogeneity) was diluted to about 50 µg protein/mL (dependent on specific activity) in 50mM-Hepes, pH7.0, 0.5M-NaCl, 20%-Glycerol, 0.05%-Triton X-100, 5mM-Dithiothreitol, 0.1mM-EDTA.

40

5x Concentrated Buffer mix was prepared using 1M-Tris-HCl (pH7.0, 1mL), 1M-MgCl<sub>2</sub> (0.16mL), 1M-Dithiothreitol (0.05mL), 5M-NaCl (0.4mL), and Water (8.4mL), Total 10mL.

Substrate Mix was prepared using 5x Concentrated Buffer mix (12 $\mu$ L), [ $^3$ H]-UTP (1  $\mu$ Ci/ $\mu$ L; 21.7 $\mu$ M, 1 $\mu$ L), 22  $\mu$ M-UTP (100  $\mu$ M, 13.2  $\mu$ L), 10  $\mu$ g/mL polyA-oligoU (100  $\mu$ g/mL, 6 $\mu$ L), and Water (12.8  $\mu$ L), *Total* 45 $\mu$ L.

- 5 The Assay was set up using Substrate Mix (45 $\mu$ L), compound (10 $\mu$ L), and Diluted Enzyme (added last to start reaction) (5 $\mu$ L), *Total* 60 $\mu$ L.

10 The reaction was performed in a U-bottomed, clear, 96-well plate. The reaction was mixed on a plate-shaker, after addition of the Enzyme, and incubated for 2h at 22°C. After this time, the reaction was stopped by addition of 25 $\mu$ L of 100mM-EDTA.

15 A DEAE Filtermat (Part No. 1205-405 from Pharmacia) was pre-washed in water and alcohol and dried. 2 x 20 $\mu$ L of the Stopped Assay Mix was spotted onto a square of the DEAE Filtermat. The DEAE Filtermat was washed for 2x 15min in SSC buffer (0.3M-NaCl, 30mM-Na Citrate) followed by 2x 2min in water and 1x 1min in alcohol. The Filtermat was dried and sealed in a bag together with 10mL of OptiScint HiSafe scintillation fluid. The radioactivity present on the filtermat was detected by scintillation counting on a Wallac 1205 Betaplate counter. After subtraction of background levels without enzyme, any reduction in the amount of radioactivity incorporated in the presence of a compound, compared to that in the absence, was taken as a measure of the level of inhibition. Ten concentrations of compounds were tested in two- or threefold dilutions. From the counts, percentage of inhibition at highest concentration tested or IC<sub>50</sub>s for the compounds were calculated using Grafit3 or Grafit4 software packages.

25 **In Vitro Detection of inhibitors of HCV RNA-dependent RNA Polymerase Activity (B)**

Incorporation of [ $^{33}$ P]-GMP into RNA was followed by absorption of the biotin labelled RNA polymer by streptavidin containing SPA beads. A synthetic template consisting of biotinylated 13mer-oligoG hybridised to polyrC was used as a homopolymer substrate.

30 Reaction Conditions were 0.5  $\mu$ M [ $^{33}$ P]-GTP (0.2 Ci/mMol), 1 mM Dithiothreitol, 20 mM MgCl<sub>2</sub>, 5mM MnCl<sub>2</sub>, 20 mM Tris-HCl, pH7.5, 1.6  $\mu$ g/mL polyC/0.256  $\mu$ M biotinylated oligoG13, 10% glycerol, 0.01% NP-40, 0.2 u/ $\mu$ L RNasin and 50 mM NaCl.

35 HCV RNA Polymerase (Recombinant full-length NS5B (Lohmann et al, J. Virol. 71 (11), 1997, 8416 'Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity') expressed in baculovirus and purified to homogeneity) was added to 10 nM final concentration.

40 5x concentrated assay buffer mix was prepared using 1M MnCl<sub>2</sub> (0.25 mL), glycerol (4mL), 10% NP-40 (0.025 mL) and Water (7.225 mL), *Total* 10 mL.

2x concentrated enzyme buffer contained 1M-Tris-HCl, pH7.5 (0.4 mL), 5M NaCl (0.2 mL), 1M-MgCl<sub>2</sub> (0.4 mL), glycerol (1 mL), 10% NP-40 (10 µL), 1M DTT (20 µL) and water (7.97 mL), Total 10 mL.

- 5 Substrate Mix was prepared using 5x Concentrated assay Buffer mix (4µL), [<sup>33</sup>P]-GTP (10 µCi/µL, 0.02µL), 25 µM GTP (0.4 µL), 0.4 u/µL RNasin (0.04 µL), 20 µg/mL polyrC/biotinylated-oligorG (1.6 µL), and Water (3.94 µL), Total 10 µL.

- 10 Enzyme Mix was prepared by adding 1mg/ml full-length NS5B polymerase (1.5 µL) to 2.811mL 2x-concentrated enzyme buffer.

The Assay was set up using compound (1µL), Substrate Mix (10 µL), and Enzyme Mix (added last to start reaction) (10 µL), Total 21 µL.

- 15 The reaction was performed in a U-bottomed, white, 96-well plate. The reaction was mixed on a plate-shaker, after addition of the Enzyme, and incubated for 1h at 22°C. After this time, the reaction was stopped by addition of 40 µL 1.875 mg/ml streptavidin SPA beads in 0.1 M EDTA. The beads were incubated with the reaction mixture for 1h at 22°C after which 120 µL 0.1 M EDTA in PBS was added. The plate was sealed, mixed centrifuged and  
20 incorporated radioactivity determined by counting in a Trilux (Wallac) or Topcount (Packard) Scintillation Counter.

- 25 After subtraction of background levels without enzyme, any reduction in the amount of radioactivity incorporated in the presence of a compound, compared to that in the absence, was taken as a measure of the level of inhibition. Ten concentrations of compounds were tested in three- or fivefold dilutions. From the counts, percentage of inhibition at highest concentration tested or IC<sub>50</sub>s for the compounds were calculated using Grafit3 or Grafit4 software packages.

- 30 The exemplified compounds all had an IC<sub>50</sub> of <50µM in one of the above described assays. Accordingly, the compounds of the invention are of potential therapeutic benefit in the treatment and prophylaxis of HCV. Preferred compounds had an IC<sub>50</sub> of <5µM.

- 35 The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example immune therapies (eg. interferon), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists,  
40 lung surfactants and/or antimicrobial and anti-viral agents (eg ribavirin and amantidine). The compositions according to the invention may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent.

5

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

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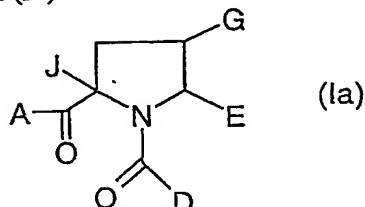
The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

15

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.

Claims

1. Compounds of Formula (Ia) :



- 5 wherein:

A represents hydroxy;

D represents aryl or heteroaryl;

- 10 E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

15

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and heteroaryl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

20

R<sup>4</sup> is selected from the group consisting of C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

- 25 R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; and

J represents C<sub>1-6</sub>alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

30

provided that i) E and G are not both hydrogen; and  
ii) the compound is other than

4-ethenyl-1-(2-nitrobenzoyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;

1-(2-aminobenzoyl)-4-(1-hydroxyethyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;

- 35 4-(1-hydroxyethyl)-1-(2-nitrobenzoyl)-2,2-pyrrolidinedicarboxylic acid, diethyl ester;

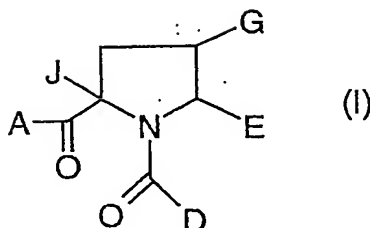
and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl.

- 5     2.     A compound as claimed in claim 1 selected from the group consisting of:  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid ;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;
- 10     *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-fluoromethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-
- 15     thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-hydroxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-allyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;
- 20     *rel*-(2S,4R,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-propyloxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-methoxymethyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-ethoxymethyl-5-(1,3-thiazol-
- 25     2-yl)pyrrolidine-2-carboxylic acid;  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropenyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid; and  
*rel*-(2S,4S,5R)-2-Isobutyl-1-(3-methoxy-4-*tert*-butylbenzoyl)-4-isopropyl-5-(1,3-thiazol-2-yl)pyrrolidine-2-carboxylic acid;

30

and salts, solvates and esters, and individual enantiomers thereof.

3.     A method of treating or preventing viral infection which comprises administering to a subject in need thereof, an effective amount of a compound of Formula (I)



wherein:

A represents hydroxy;

5 D represents aryl or heteroaryl;

E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

10 G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

15 R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and heteroaryl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

20 R<sup>4</sup> is selected from the group consisting of C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; and

25 J represents C<sub>1-6</sub>alkyl, heterocyclalkyl, arylalkyl or heteroarylalkyl;

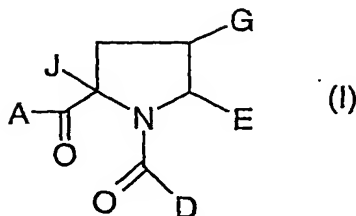
and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl.

30

4. A method as claimed in claim 3 which involves inhibiting HCV.

5. A method as claimed in claim 3 in which the compound is administered in an oral  
35 dosage form.

6. A compound of Formula (I)



wherein:

A represents hydroxy;

D represents aryl or heteroaryl;

E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and heteroaryl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R<sup>4</sup> is selected from the group consisting of C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; and

J represents C<sub>1-6</sub>alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

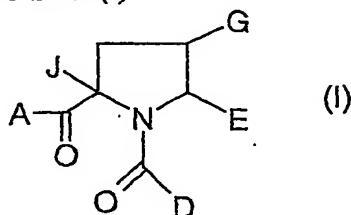
and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl;

for use in medical therapy.

7. A compound as claimed in claim 6 wherein the medical therapy is the treatment of viral infection.

8. A compound as claimed in claim 7 wherein the viral infection is HCV.

9. Use of a compound of Formula (I)



5 wherein:

A represents hydroxy;

D represents aryl or heteroaryl;

10 E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl;

G represents hydrogen or C<sub>1-6</sub>alkyl optionally substituted by one or more substituents selected from halo, OR<sup>1</sup>, SR<sup>1</sup>, C(O)NR<sup>2</sup>R<sup>3</sup>, C(O)R<sup>4</sup>, CO<sub>2</sub>R<sup>4</sup>, NR<sup>2</sup>R<sup>3</sup>, NHC(O)R<sup>4</sup>, NHCO<sub>2</sub>R<sup>4</sup>, NHC(O)NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, SO<sub>2</sub>R<sup>4</sup>, nitro, cyano and heterocyclyl;

15

R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, arylalkyl, or heteroarylalkyl;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, C<sub>1-6</sub>alkyl, aryl and heteroaryl; or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

20

R<sup>4</sup> is selected from the group consisting of C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

25 R<sup>5</sup> and R<sup>6</sup> are independently selected from the group consisting of hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group; and

J represents C<sub>1-6</sub>alkyl, heterocyclylalkyl, arylalkyl or heteroarylalkyl;

30

and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other than *tert*-butyl;

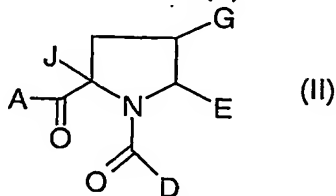
in the manufacture of a medical for the treatment of viral infection.

35

10. Use as claimed in claim 9, wherein the viral infection is HCV.

11. A pharmaceutical formulation comprising a compound of Formula (I) in conjunction with a pharmaceutically acceptable diluent or carrier.

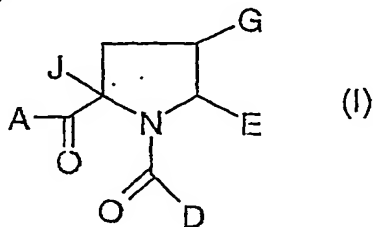
12. A process for the preparation of a compound of Formula (I) as defined in claim 3,  
5 comprising treatment of a compound of Formula (II)



in which A is *tert*-butoxy, and D, E, G and J are as defined for Formula (I), with an acid.

ABSTRACT OF THE DISCLOSURE

## 5 Anti-viral agents of Formula (I)



wherein:

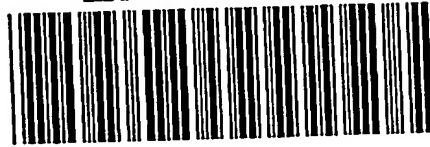
10 A represents hydroxy; D represents aryl or heteroaryl; E represents hydrogen, C<sub>1-6</sub>alkyl, aryl, heteroaryl or heterocyclyl; G represents hydrogen or C<sub>1-6</sub>alkyl; J represents C<sub>1-6</sub>alkyl, heterocyclalkyl, arylalkyl or heteroarylalkyl;

and salts, solvates and esters thereof; provided that when A is esterified to form -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, then R is other  
15 than *tert*-butyl;

processes for their preparation and methods of using them in HCV treatment are provided.

PCT Application

**EP0311813**



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